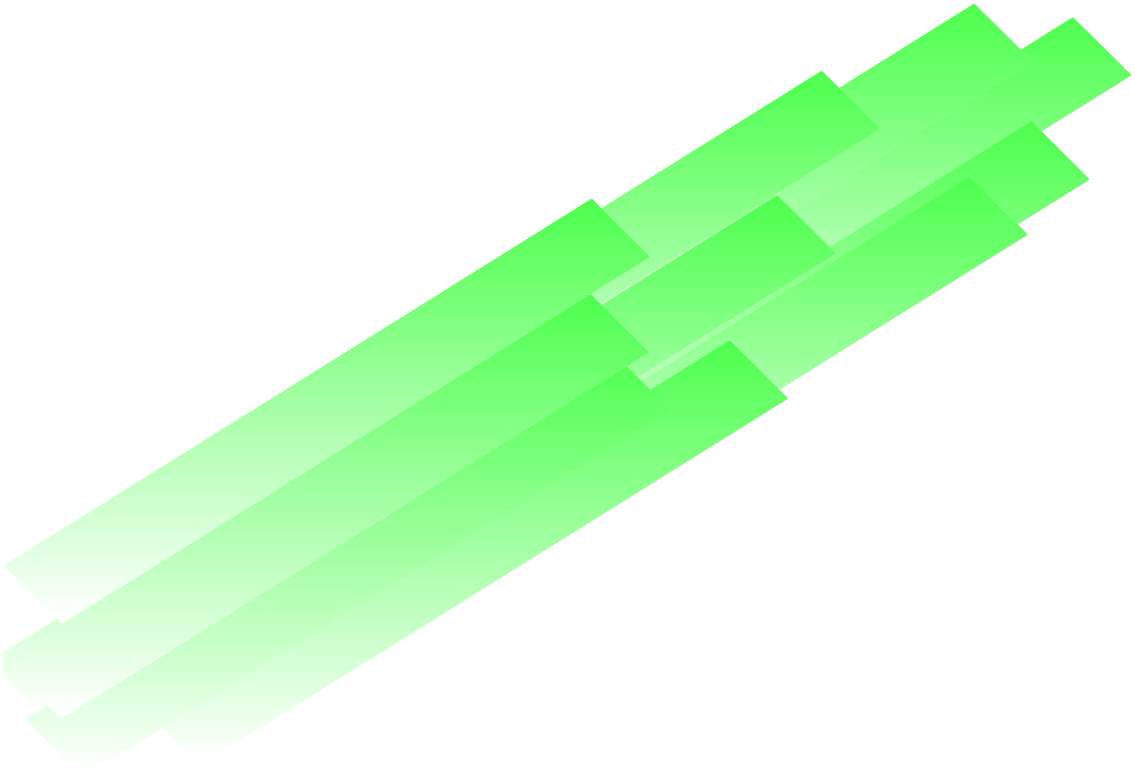
Guidance for Industry

Labeling Guidance for Paclitaxel Injection



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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GUIDANCE FOR INDUSTRY[1]

Labeling Guidance for Paclitaxel Injection

I. INTRODUCTION

This guidance describes the recommended labeling to comply with 21 CFR 314.94(a)(8)(iv) for an abbreviated new drug application. The basis of this guidance is the approved labeling of the reference listed drug (TAXOL®; Bristol Myers Squibb Pharmaceutical Research Institute; 20-262/S-022; Approved August 4, 1997; Revised July 25, 1997). Differences between the reference listed drug and this guidance may exist and may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, or omission of an indication or other aspects of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the Federal Food, Drug, and Cosmetic Act.

II. LABELING

[See next page.]

[1]This guidance has been prepared by the Office of Generic Drugs, Division of Labeling and Program Support in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the development of labeling for an abbreviated new drug application. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

PACLITAXEL INJECTION

WARNINGS

Paclitaxel injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H_2 antagonists. (See DOSAGE AND ADMINISTRATION section.) Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

Paclitaxel therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving paclitaxel.

DESCRIPTION

Paclitaxel is a natural product with antitumor activity. Paclitaxel is obtained via a semi-synthetic process from *Taxus Baccata*. The chemical name for paclitaxel is (2a*R*,4*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-1,2a,3,4,4a,6,9,10,11,12,12a,12b-Dodecahydro-4,6,9,11,12,-12b-hexahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5*H*-cyclodeca[3,4]benz[1,2-*b*]oxet-5-one 6,12b-diacetate,12-benzoate, 9-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

Paclitaxel is a white to off-white crystalline powder and is highly lipophilic, insoluble in water, and melts at around 216 to 217°C. It has a molecular weight of 853.93 and a molecular formula $C_{47}H_{51}NO_{14}$. Paclitaxel has the following structural formula:

[INSERT STRUCTURAL FORMULA HERE]

Paclitaxel Injection is a clear colorless to slightly yellow viscous solution intended for intravenous administration. It is supplied as a sterile nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Each mL of sterile nonpyrogenic solution contains 6 mg of paclitaxel, 527 mg of polyoxyethylated caster oil and 49.7% (v/v) dehydrated alcohol, USP.

CLINICAL PHARMACOLOGY

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Following intravenous administration of paclitaxel injection, paclitaxel plasma concentrations declined in a biphasic manner. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment.

Pharmacokinetic parameters of paclitaxel following 3 and 24 hour infusions of paclitaxel at dose levels of 135 and 175 mg/m^2 were determined in a Phase 3 randomized study in ovarian cancer patients and are summarized in the following table:

SUMMARY OF PHARMACOKINETIC PARAMETERS - MEAN VALUES

DOSE (mg/m^2)	INFUSION DURATION(h)	N (PATIENTS)	C_{MAX} (ng/mL)	AUC (0-∞) (ng·h/mL)	T-HALF (h)	CL_T (L/h/m^2)
135	24	2	195	6300	52.7	21.7
175	24	4	365	7993	15.7	23.8
135	3	7	2170	7952	13.1	17.7
175	3	5	3650	15007	20.2	12.2

Cmax = Maximum plasma concentration
AUC (0-∞) = Area under the plasma concentration-time curve from time 0 to infinity
CL_T = Total body clearance

It appeared that with the 24 hour infusion of paclitaxel, a 30% increase in dose (135 mg/m^2 versus 175 mg/m^2) increased the Cmax by 87%, whereas the AUC(0-∞) remained proportional. However, with a 3 hour infusion, for a 30% increase in dose, the Cmax and AUC(0-∞) were increased by 68% and 89%, respectively. The mean apparent volume of distribution at steady state, with the 24 hour infusion of paclitaxel ranged from 227 to 688 L/m^2, indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetics of paclitaxel were also evaluated in adult cancer patients who received single doses of 15-135 mg/m^2 given by 1 hour infusions (n=15), 30 to 275 mg/m^2 given by 6 hour infusions (n=36), and 200 to 275 mg/m^2 given by 24 hour infusions (n=54) in Phase 1 & 2 studies. Values for CL_T and volume of distribution were consistent with the findings in the Phase 3 study.

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 g/mL, indicate that between 89 to 98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

After intravenous administration of 15 to 275 mg/m^2 doses of paclitaxel as 1, 6, or 24 hour infusions, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3% to 12.6% of the dose, indicating extensive non-renal clearance. In five patients administered a 225 or 250 mg/m^2 dose of radio-labeled paclitaxel as a 3 hour infusion, a mean of 71% of the radioactivity was excreted in the feces in 120 hours, and 14% was recovered in the urine. Total recovery of radioactivity ranged from 56% to 101% of the dose. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces, while metabolites, primarily 6∝-hydroxypaclitaxel, accounted for the balance. *In vitro* studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6∝-hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6∝-3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6∝-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17∝-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2CB, also inhibited the formation of 6∝-hydroxypaclitaxel *in vitro.* The pharmacokinetics of paclitaxol may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2CB and/or CYP3A4. (See PRECAUTIONS - Drug Interactions suction.) The effect of renal or hepatic dysfunction on the disposition of paclitaxel has not been investigated.

Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

Clinical Studies:
OVARIAN CARCINOMA: Data from five Phase 1 and 2 clinical studies (189 patients), a multicenter, randomized Phase 3 study (407 patients), as well as an interim analysis of data from more than 300 patients enrolled in a treatment referral center program were used in support of the use of paclitaxel injection in patients who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary. Two of the Phase 2 studies (92 patients) utilized an initial dose of 135 to 170 mg/m^2 in most patients (>90%) administered over 24 hours by continuous infusion. Response rates in these two studies were 22% (95% CI = 11 to 37%) and 30% (95% CI = 18 to 46%) with a total of six complete and 18 partial responses in 92 patients. The median duration of overall response in these two studies measured from the first day of treatment was 7.2 months (range: 3.5 to 15.8 months) and 7.5 months (range: 5.3 to 17.4 months), respectively. The median survival was 8.1 months (range: 0.2 to 36.7 months) and 15.9 months (range: 1.8 to 34.5+ months).

The Phase 3 study had a bifactorial design and compared the efficacy and safety of paclitaxel, administered at two different doses (135 or 175 mg/m^2) and schedules (3 or 24 hour infusion). The overall response rate for the 407 patients was 16.2% (95% CI = 12.8 to 20.2%), with 6 complete and 60 partial responses. Duration of response, measured from the first day of treatment was 8.3 months (range: 3.2 to 21.6 months). Median time to progression was 3.7 months (range: 0.1+ to 25.1+ months). Median survival was 11.5 months (range: 0.2 to 26.3+ months).

Response rates, median survival and median time to progression for the 4 arms are given in the following table.

EFFICACY IN THE PHASE 3 STUDY

	175/3 (n=96)	175/24 (n=106)	135/3 (n=99)	135/24 (n=106)
• ***Response***				
- rate (percent)	14.6	21.7	15.2	13.2
- 95% Confidence Interval	(8.5-23.6)	(14.5-31.0)	(9.0-24.1)	(7.7-21.5)
• ***Time to Progression***				
- median (months)	4.4	4.2	3.4	2.8
- 95% Confidence Interval	(3.0-5.6)	(3.5-5.1)	(2.8-4.2)	(1.9-4.0)
• ***Survival***				
- median (months)	11.5	11.8	13.1	10.7
- 95% Confidence Interval	(8.4-14.4)	(8.9-14.6)	(9.1-14.6)	(8.1-13.6)

Analyses were performed as planned by the study protocol, by comparing the two doses (135 or

175 mg/m^2) irrespective of the schedule (3 or 24 hours) and the two schedules irrespective of dose. Patients receiving the 175 mg/m^2 dose achieved a higher response rate than those receiving the 135 mg/m^2 dose: 18% vs. 14% (p=0.28). No difference in response rate was detected when comparing the 3 hour with the 24 hour infusion: 15% vs. 17% (p=0.50). Patients receiving the 175 mg/m^2 dose of paclitaxel had a longer time to progression than those receiving the 135 mg/m^2 dose: median 4.2 vs. 3.1 months (p=0.03). Time to progression was longer for patients receiving the 3 hour vs. the 24 hour infusion: 4.0 months vs. 3.7 months (p=0.08). No difference in survival according to dose or schedule was observed. These statistical analyses should be viewed with caution because of the multiple comparisons made.

Paclitaxel remained active in patients who had developed resistance to platinum-containing therapy (defined as tumor progression while on, or tumor relapse within 6 months from completion of, platinum containing regimen) with response rates of 14% in the Phase 3 study and 31% in the Phase 1 & 2 clinical studies.

The adverse event profile in the Phase 3 study was consistent with that seen for a pooled analysis performed on 812 patients treated in ten clinical studies (see ADVERSE REACTIONS section). For the 403 patients who received paclitaxel injection in the Phase 3 study, the following table shows the incidence of several important adverse events.

FREQUENCY OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 STUDY					
		PERCENT OF PATIENTS			
		175/3 (n=95)	175/24 (n=105)	135/3 (n=98)	135/24 (n=105)
• ***Bone Marrow***					
- Neutropenia	<2,000/mm^3	78	98	78	98
	<500/mm^3	27	75	14	67
- Thrombocytopenia	<100,000/mm^3	4	18	8	6
	<50,000/mm^3	1	7	2	1
- Anemia	<11 g/dL	84	90	68	88
	<8 g/dL	11	12	6	10
- Infections		26	29	20	18
• ***Hypersensitivity Reaction****					
- All		41	45	38	45
- Severe		2	0	2	1
• ***Peripheral Neuropathy***					
- Any symptoms		63	60	55	42
- Severe symptoms		1	2	0	0
• ***Mucositis***					
- Any symptoms		17	35	21	25
- Severe symptoms		0	3	0	2

* *All patients received premedication*

Myelosuppression was dose and schedule related, with the schedule effect being more prominent. The development of severe hypersensitivity reactions (HSRs) was rare; 1% of the patients and 0.2% of the courses overall. There was no apparent dose or schedule effect seen for the HSRs. Peripheral neuropathy was clearly dose-related, but schedule did not appear to affect the incidence.

The results of the randomized study support the use of paclitaxel at doses of 135 or 175 mg/m^2, administered by a 3 hour intravenous infusion. The same doses administered by 24 hour infusion were more toxic.

BREAST CARCINOMA: Data from 83 patients accrued in three phase 2 open label studies and from 471 patients enrolled in a phase 3 randomized study were available to support the use of paclitaxel in patients with metastatic breast carcinoma.

Phase 2 Open Label Studies: Two studies were conducted in 53 patients previously treated with a maximum of one prior chemotherapeutic regimen. Paclitaxel was administered in these 2 trials as a 24 hour infusion at initial doses of 250 mg/m^2 (with G-CSF support) or 200 mg/m^2. The response rates were 57% (95% CI: 37-75%) and 52% (95% CI: 32-72%), respectively. The third phase 2 study was conducted in extensively pretreated patients who had failed anthracycline therapy and who had received a minimum of 2 chemotherapy regimens for the treatment of metastatic disease. The dose of paclitaxel was 200 mg/m^2 as a 24 hour infusion with G-CSF support. Nine of the 30 patients achieved a partial response, a response rate of 30% (95% CI: 15-50%).

Phase 3 Randomized Study: This multicenter trial was conducted in patients previously treated with one or two regimens of chemotherapy. Patients were randomized to receive paclitaxel injection at a dose of either 175 mg/m^2 or 135 mg/m^2 given as a 3 hour infusion. In the 471 patients enrolled, 60% had symptomatic disease with impaired performance status at study entry, and 73% had visceral metastases. These patients had failed prior chemotherapy either in the adjuvant setting (30%), the metastatic setting (39%), or both (31%). Sixty-seven percent of the patients had been previously exposed to anthracyclines and 23% of them had disease considered resistant to this class of agents.

The overall response rate for the 454 evaluable patients was 26% (95% CI: 22-30%), with 17 complete and 99 partial responses. The median duration of response, measured from the first day of treatment, was 8.1 months (range: 3.4-18.1+ months). Overall for the 471 patients, the median time to progression was 3.5 months (range: 0.03-17.1 months). Median survival was 11.7 months (range: 0-18.9 months).

Response rates, median survival and median time to progression for the 2 arms are given in the following table.

EFFICACY IN THE PHASE 3 STUDY		
	175/3 (n=235)	135/3 (n=236)
• ***Response***		
- rate (percent)	28	22
- 95% Confidence Interval	(22-34)	(17-27)
• ***Time to Progression***		
- median (months)	4.2	3.0
- 95% Confidence Interval	(3.2-4.6)	(2.5-3.8)
• ***Survival***		
- median (months)	11.7	10.5
- 95% Confidence Interval	(10.0-13.8)	(9.0-12.8)

For the 458 patients who received paclitaxel injection in the Phase 3 study, the following table shows the incidence of several important adverse events by treatment arm (each arm was administered by a 3 hour infusion).

FREQUENCY OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 BREAST CARCINOMA STUDY		
	Percent of Patients	
	175mg/m^2 (n=229)	135 mg/m^2 (n=229)
• ***Bone Marrow***		
- Neutropenia* <2,000/mm^3	90	81
<500/mm^3	28	19
- Thrombocytopenia*<100,000/mm^3	11	7
<50,000/mm^3	3	2
- Anemia <11 g/dL	55	47
<8 g/dL	4	2
- Infections	23	15
- Febrile Neutropenia	2	2
• ***Hypersensitivity Reaction****		
- All	36	31
- Severe	0	<1
• ***Peripheral Neuropathy***		
- Any symptoms	70	46
- Severe symptoms	7	3
• ***Mucositis***		
- Any symptoms	23	17
- Severe symptoms	3	<1

**Based on worst course analysis*

*** All patients received premedication*

Myelosuppression and peripheral neuropathy were dose related. There was one severe hypersensitivity reaction (HSR) observed at the dose of 135 mg/m^2.

INDICATIONS AND USAGE

Paclitaxel injection is indicated, after failure of first-line or subsequent chemotherapy for the treatment of metastatic carcinoma of the ovary.

Paclitaxel injection is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

CONTRAINDICATIONS

Paclitaxel injection is contraindicated in patients who have a history of hypersensitivity reactions to paclitaxel or other drugs formulated in polyoxyethylated castor oil.

Paclitaxel should not be used in patients with solid tumors who have baseline neutrophil counts of <1500 cells/mm^3.

WARNINGS

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% of patients receiving paclitaxel injection in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H_2 antagonists. (See DOSAGE AND ADMINISTRATION section). Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. Neutrophil nadirs occurred at a median of 11 days. Paclitaxel should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm^3. Frequent monitoring of blood counts should be instituted during paclitaxel treatment. Patients should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level >1500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3.

Severe conduction abnormalities have been documented in <1% of patients during paclitaxel therapy and in some cases requiring pacemaker placement. If patients develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

Pregnancy: Paclitaxel can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/m^2 basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions and increased fetal deaths. Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1 mg/kg/day (about 1/15 the daily maximum recommended human dose on a mg/m^2 basis); teratogenic potential could not be assessed at higher doses due to extensive fetal mortality.

There are no adequate and well-controlled studies in pregnant women. If paclitaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP
[di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

Drug Interactions: In a Phase 1 trial using escalating doses of paclitaxel (110 to 200 mg/m^2) and cisplatin (50 or 75 mg/m^2) given as sequential infusions, myelosuppression was more profound when paclitaxel was given after cisplatin than with the alternate sequence (i.e., paclitaxel before cisplatin). Pharmacokinetic data from these patients demonstrated a decrease in paclitaxel clearance of approximately 33% when paclitaxel injection was administered following cisplatin.

The metabolism of paclitaxil is catalyzed by cytochrome P450 isoenzymes CYP2CB and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2CB and CYP3A4. (See CLINICAL PHARMACOLOGY section.)

Potential interactions between paclitaxel, a substrate of CYP3A4 and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4 have not been evaluated in clinical trials.

Reports in the literature suggest that plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination.

Hematology: Paclitaxel therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving paclitaxel. Patients should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3 for seven days or more) during a course of paclitaxel therapy, a 20% reduction in dose for subsequent courses of therapy is recommended.

Hypersensitivity Reactions: Patients with a history of severe hypersensitivity reactions to products containing polyoxyethylated castor oil (e.g., cyclosporin for injection concentrate and teniposide for injection concentrate) should not be treated with paclitaxel injection. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with paclitaxel should be premedicated with corticosteroids (such as dexamethasone), diphenhydramine and H_2 antagonists (such as cimetidine or ranitidine). Minor symptoms such as flushing, skin reactions, dyspnea, hypotension or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with paclitaxel.

Cardiovascular: Hypotension, bradycardia, and hypertension have been observed during administration of paclitaxel, but generally do not require treatment. Occasionally paclitaxel infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of paclitaxel infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities. (See WARNINGS section.)

Nervous System: Although, the occurrence of peripheral neuropathy is frequent, the development of severe symptomatology is unusual and requires a dose reduction of 20% for all subsequent courses of paclitaxel.

Paclitaxel contains dehydrated alcohol USP, 396 mg/mL; consideration should be given to possible CNS and other effects of alcohol. (See PRECAUTIONS - Pediatric Use section).

Hepatic: There is evidence that the toxicity of paclitaxel is enhanced in patients with elevated liver enzymes. Caution should be exercised when administering Paclitaxel to patients with moderate to severe hepatic impairment and dose adjustments should be considered.

Injection Site Reaction: Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24 hour infusion than with the 3 hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxil at a different site, i.e., "recall"' as been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been received as part of the continuing surveillance of paclitaxil safety. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to ten days.

A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of paclitaxel has not been studied.

Paclitaxel has been shown to be clastogenic *in vitro* (chromosomal aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test or CHO/HGPRT gene mutation assay.

Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats at doses equal to or greater than 1 mg/kg/day (about 0.04 the daily maximum recommended human dose on a mg/m^2 basis). At this dose, paclitaxel caused reduced fertility and reproductive indices, and increase embryo- and fetotoxicity (See WARNINGS).

Pregnancy: Teratogenic Effects, Pregnancy Category D (See WARNINGS section.)

Nursing Mothers: It is not known whether the drug is excreted in human milk. Following intravenous administration of carbon-14 labeled paclitaxel to rats on days 9 to 10 postpartum, milk concentrations of radioactivity exceeded and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving paclitaxel therapy.

Pediatric Use: The safety and effectiveness of paclitaxel in pediatric patients have not been established.

There have been reports of central nervous system (CNS) toxicity in an ongoing investigational clinical trial in pediatric patients in which paclitaxel was infused intravenously over 3 hours at doses ranging from 350 mg/m^2 to 420 mg/m^2. The toxicity is most likely attributable to the high dose of the ethanol component of the paclitaxil vehicle given over a short infusion time. The use of concomitant antihistamines may intensify this effect. Although a direct effect of the paclitaxel itself cannot be discounted, the high doses used in this study (over twice the recommended adult dosage) must be considered in assessing the safety of paclitaxol for use in this population.

ADVERSE REACTIONS

Data in the following table are based on the experience of 812 patients (493 with ovarian carcinoma and 319 with breast carcinoma) enrolled in 10 studies. Two hundred and seventy-five patients were treated in 8 Phase 2 studies with paclitaxel doses ranging from 135 to 300 mg/m^2 administered over 24 hours (in 4 of these studies, G-CSF was administered as hematopoietic support). Three hundred and one patients were treated in the randomized Phase 3 ovarian carcinoma study which compared two doses (135 or 175 mg/m^2) and two schedules (3 or 24 hours) of paclitaxel. Two hundred and thirty-six patients with breast carcinoma received paclitaxel (135 or 175 mg/m^2) administered over 3 hours in a controlled study.

SUMMARY OF ADVERSE EVENTS IN 812 PATIENTS RECEIVING PACLITAXEL

	% INCIDENCE
• ***Bone Marrow***	
- Neutropenia <2,000/mm^3	90
<500/mm^3	52
- Leukopenia <4,000/mm^3	90
<1,000/mm^3	17
- Thrombocytopenia <100,000/mm^3	20
<50,000/mm^3	7
- Anemia <11 g/dL	78
<8 g/dL	16
- Infections	30
- Bleeding	14
- Red Cell Transfusions	25
- Platelet Transfusions	2
• ***Hypersensitivity Reaction****	
- All	41
- Severe	2

• ***Cardiovascular***	
- Vital Sign Changes**	
- Bradycardia (N=537)	3
- Hypotension (N=532)	12
- Significant Cardiovascular Events	1
• ***Abnormal Ecg***	
- All Pts	23
- Pts with normal baseline (N=559)	14
• ***Peripheral Neuropathy***	
- Any	60
- Severe	3
• ***Myalgia/arthralgia***	
- Any	60
- Severe	8
• ***Gastrointestinal***	
- Nausea and vomiting	52
- Diarrhea	38
- Mucositis	31
• ***Alopecia***	87
• ***Hepatic*** (Pts with normal baseline and on study data)	
- Bilirubin elevations (N=765)	7
- Alkaline phosphatase elevations (N=575)	22
- AST (SGOT) elevations (N=591)	19
• ***Injection Site Reaction***	13
• ***Alopecia***	87
• ***Hepatic*** (Pts with normal baseline and on study data)	
- Bilirubin elevations (N=765)	7
- Alkaline phosphatase elevations (N=575)	22
- AST (SGOT) elevations (N=591)	19
• ***Injection Site Reaction***	13

* *All patients received premedication*
** *During the first 3 hours of infusion*

None of the observed toxicities were clearly influenced by age.

The following discussion refers to the overall safety database of 812 patients with solid tumors treated in clinical studies. The frequency and severity of adverse events have been generally similar for patients receiving paclitaxel for the treatment of ovarian or breast carcinoma. The frequency and severity of important adverse events for the Phase 3 ovarian and breast carcinoma studies are presented in tabular form by treatment arm in the "CLINICAL PHARMACOLOGY - Clinical Studies" section.

Hematologic: Bone marrow suppression was the major dose-limiting toxicity of paclitaxel. Neutropenia, the most important hematologic toxicity, was dose and schedule dependent and was generally rapidly reversible. Among patients treated in the Phase 3 ovarian study with a 3 hour infusion, neutrophil counts decline below 500 cells/mm^3 in 13% of the patients treated with a dose of 135 mg/m^2 compared to 27% at a dose of 175 mg/m^2 ($p=0.05$). In the same study, severe neutropenia (<500 cells/mm^3) was more frequent with the 24-hour than with the 3 hour infusion; infusion duration had a greater impact on myelosuppression than dose. Neutropenia did not appear to increase with cumulative exposure and did not appear to be more frequent nor more severe for patients previously treated with radiation therapy.

Fever was frequent (12% of all treatment courses). Infectious episodes occurred in 30% of all patients and 9% of all courses; these episodes were fatal in 1% of all patients, and included sepsis, pneumonia and peritonitis. In the Phase 3 ovarian study, infectious episodes were reported in 19% of the patients given either 135 or 175 mg/m^2 dose by a 3 hour infusion. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications.

Thrombocytopenia was uncommon, and almost never severe (<50,000 cells/mm^3). Twenty percent of the patients experienced a drop in their platelet count below 100,000 cells/mm^3 at least once while on treatment; 7% had a platelet count <50,000 cells/mm^3 at the time of their worst nadir. Among the 812 patients, bleeding episodes were reported in 4% of all courses and by 14% of all patients but most of the hemorrhagic episodes were localized and the frequency of these events was unrelated to the paclitaxel dose and schedule. In the Phase 3 ovarian study, bleeding episodes were reported in 10% of the patients receiving either the 135 or 175 mg/m^2 dose given by a 3 hour infusion; no patients treated with the 3 hour infusion received platelet transfusions.

Anemia (Hb<11 g/dL) was observed in 78% of all patients and was severe (Hb <8 g/dL) in 16% of the cases. No consistent relationship between dose or schedule and the frequency of anemia was observed. Among all patients with normal baseline hemoglobin, 69% became anemic on study but only 7% had severe anemia. Red cell transfusions were required in 25% of all patients

and in 12% of those with normal baseline hemoglobin levels.

Hypersensitivity Reactions (HSRs): All patients received premedication prior to paclitaxel injection (See WARNINGS and PRECAUTIONS - Hypersensitivity Reactions sections). The frequency and severity of HSRs were not affected by the dose or schedule of paclitaxel administration. In the Phase 3 ovarian study the 3 hour infusion was not associated with a greater increase in HSRs when compared to the 24 hour infusion. Hypersensitivity reactions were observed in 20% of all courses and in 41% of all patients. These reactions were severe in less than 2% of the patients and 1% of the courses. No severe reactions were observed after course 3 and severe symptoms occurred generally within the first hour of paclitaxel infusion. The most frequent symptoms observed during these severe reactions were dyspnea, flushing, chest pain and tachycardia.

The minor hypersensitivity reactions consisted mostly of flushing (28%), rash (12%), hypotension (4%), dyspnea (2%), tachycardia (2%) and hypertension (1%). The frequency of hypersensitivity reactions remained relatively stable during the entire treatment period.

Cardiovascular: Hypotension, during the first 3 hours of infusion, occurred in 12% of all patients and 3% of all courses administered. Bradycardia, during the first 3 hours of infusion, occurred in 3% of all patients and 1% of all courses. In the Phase 3 ovarian study, neither dose nor schedule had an effect on the frequency of hypotension and bradycardia. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation. The frequency of hypotension and bradycardia were not influenced by prior anthracycline therapy.

Significant cardiovascular events possibly related to paclitaxel occurred in approximately 1% of all patients. These events included syncope, rhythm abnormalities, hypertension and venous thrombosis. One of the patients with syncope treated with paclitaxel at 175 mg/m^2 over 24 hours had progressive hypotension and died. The arrhythmias included asymptomatic ventricular tachycardia, bigeminy and complete AV block requiring pacemaker placement.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 23% of all patients. Among patients with a normal ECG prior to study entry, 14% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, sinus tachycardia and premature beats. Among patients with normal ECG at baseline, prior therapy with anthracyclines did not influence the frequency of ECG abnormalities.

Cases of myocardial infarction have been reported rarely. Congestive heart failure has been reported typically in patients who have received other chemotherapy, notably anthracyclines.

(See PRECAUTIONS - Drug Interactions section)

Rare reports of atrial fibrillation and supraventricular tachycardia have been received as part of the continuing surveillance of paclitaxel safety.

Respiratory: Rare reports of interstitial pneumonia, lund fibrosis and pulmonary embolism have been received as part of the continuing surveillance of paclitaxol safety.

Neurologic: The frequency and severity of neurologic manifestations were dose-dependent, but were not influenced by infusion duration. Peripheral neuropathy was observed in 60% of all patients (3% severe) and in 52% (2% severe) of the patients without pre-existing neuropathy.

The frequency of peripheral neuropathy increased with cumulative dose. Neurologic symptoms were observed in 27% of the patients after the first course of treatment and 34 to 51% from course 2 to 10.

Peripheral neuropathy was the cause of paclitaxel discontinuation in 1% of all patients. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. The incidence of neurologic symptoms did not increase in the subset of patients previously treated with cisplatin. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy.

Other than peripheral neuropathy, serious neurologic events following paclitaxel administration have been rare (<1%) and have included grand mal seizures, syncope, ataxia and neuroencephalopathy.

Rare reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of paclitaxel safety. Optic nerve and/or visual disturbances (scintillating scotomata) have also been reported, particularly in patients who have received higher doses than those recommended. These effects generally have been reversible. However, rare reports in the literature of abnormal visual evoked potentials in patients have suggested persistent optic nerve damage.

Arthralgia/Myalgia: There was no consistent relationship between dose or schedule of paclitaxel and the frequency or severity of arthralgia/myalgia. Sixty percent of all patients treated experienced arthralgia/myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred two or three days after paclitaxel administration, and resolved within a few days. The frequency and severity of musculoskeletal symptoms remained unchanged throughout the treatment period.

Hepatic: No relationship was observed between liver function abnormalities and either dose or schedule of paclitaxel administration. Among patients with normal baseline liver function 7%,

22% and 19% had elevations in bilirubin, alkaline phosphatase and AST (SGOT), respectively. Prolonged exposure to paclitaxel was not associated with cumulative hepatic toxicity.

Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel safety.

Gastrointestinal (GI): Nausea/vomiting, diarrhea and mucositis were reported by 52%, 38% and 31% of all patients, respectively. These manifestations were usually mild to moderate. Mucositis was schedule dependent and occurred more frequently with the 24 hour than with the 3 hour infusion.

Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, ischemic colitis, and dehydration have been received as part of the continuing surveillance of paclitaxel safety. Rare reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were observed in patients treated with paclitaxel alone and in combination with other chemotherapeutic agents.

Injection Site Reaction: Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24 hour infusion than with the 3 hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site, i.e., "recall", has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been received as part of the continuing surveillance of paclitaxel safety. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to ten days.

A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Other Clinical Events: Alopecia was observed in almost all (87%) of the patients. Transient skin changes due to paclitaxel related hypersensitivity reactions have been observed, but no other skin toxicities were significantly associated with paclitaxel administration. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon (2%). Edema was reported in 21% of all patients (17% of those without baseline edema); only 1% had severe edema and none of these patients required treatment discontinuation. Edema was most commonly focal and disease related. Edema was observed in 5% of all courses for patients with normal baseline and did not increase with time on study.

Rare reports of skin abnormalities related to radiation recall have been received as part of the

continuing surveillance of paclitaxel safety.

Rare reports of radiation pneumonitis have been received in patients receiving concurrent radiotherapy.

Accidental Exposure: Upon inhalation, dyspnea, chest pain, burning eyes, sore throat and nausea have been reported. Following topical exposure, events have included tingling, burning and redness.

OVERDOSAGE

There is no known antidote for paclitaxel overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis.

DOSAGE AND ADMINISTRATION

Note: Contact of the undiluted concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted paclitaxel injection solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

All patients should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel.

In patients with carcinoma of the ovary, paclitaxel has been used at several doses and schedules; however, the optimal regimen is not yet clear (see CLINICAL PHARMACOLOGY section). In patients previously treated with chemotherapy for ovarian cancer, the recommended regimen is paclitaxel 135 mg/m^2 or 175 mg/m^2 administered intravenously over three hours every three weeks.

For patients with carcinoma of the breast, paclitaxel at a dose of 175 mg/m^2 administered intravenously over 3 hours every three weeks has been shown to be effective after failure of chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.

For the therapy of patients with solid tumors(ovary and breast), courses of paclitaxel should not be repeated until the neutrophil count is at least 100,000 cells/mm^3. Patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer) or severe peripheral

neuropathy during paclitaxel therapy should have dosage reduced by 20% for subsequent courses of paclitaxel. The incidence of neurotoxicity and the severity of neutropenia increase with dose.

Preparation and Administration Precautions: Paclitaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling paclitaxel injection. The use of gloves is recommended. If paclitaxel solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning and redness. If paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat and nausea have been reported.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration (See PRECAUTIONS - Injection Site Reaction section).

Preparation for Intravenous Administration: Paclitaxel injection must be diluted prior to infusion. Paclitaxel injection should be diluted in 0.9% Sodium Chloride Injection, 5% Dextrose Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25° C) and room lighting conditions.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line (0.22 micron) filter.

Data collected for the presence of the extractable plasticizer DEHP [di-(2-ethylhexyl)phthalate] show that levels increase with time and concentration when dilutions are prepared in PVC containers. Consequently, the use of plasticized PVC containers and administration sets is not recommended. Paclitaxel solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVC containing administration sets, such as those which are polyethylene-lined, should be used.

Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

The Chemo Dispensing Pin™ device or similar devices with spikes should not be used with vials of paclitaxel injection since they can cause the stopper to collapse resulting in the loss of sterile integrity of the paclitaxel solution.

Stability: Unopened vials of paclitaxel injection are stable until the date indicated on the

package when stored between 2° to 8° C (36° to 46° F), in the original package. Freezing does not adversely affect the product. Upon refrigeration components in the paclitaxel injection may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on product quality under these circumstances. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded. Solutions for infusion prepared as recommended are stable at ambient temperature (approximately 25° C) and lighting conditions for up to 27 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

- Established Name
- Strength of dosage form
- Packaging, NDC number
- Dosage form
- Store the vials in original cartons between 2° and 25° C (36° to 77°F). Retain in the original carton to protect from light.
- "Caution: Federal Law..." statement.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published[1-7]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. JAMA 1985; 253 (11): 1590-1592.
3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts, 02115.
4. Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia 1983; 1:426-428.
5. Jones RB, et al: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA-A Cancer Journal for Clinicians 1983; Sept/Oct 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm 1990; 47:1033-1049.

7. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. Am J Hosp Pharm 1986; 43:1193-1204.

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Include the following information at the end of the insert:

- Date of latest revision.
- "Manufactured by" statement. - Should be consistent with container labels and/or carton labeling.

CONTAINER/CARTON LABEL

In addition to the general label requirements ("Caution: Federal Law..." statement, statement of net quantity, etc.) please include the following:

Main Panel:

- The established name and strength should read as follows:

  PACLITAXEL INJECTION

  30 mg/5 mL or 100 mg/16.7 mL
  (6 mg/mL)

- CAUTION: Dilution required. Read enclosed package insert.
- WARNING: Cytotoxic agent
- Multiple Dose Vial

Side Panel:

- Each mL contains statement should read as follows:

  Each mL of sterile nonpyrogenic solution contains 6 mg of paclitaxel. In addition, each mL contains 527 mg of polyoxyethylated caster oil and 49.7% (v/v) dehydrated alcohol, USP.

- Store the vials in original cartons between 2° to 25° C (36° to 77°F). Retain in carton until time of use to protect from light.

- "Usual Dosage" statement should read as follows:

  Usual Dosage: Read accompanying circular for detailed dosage directions for use and precautions.